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EXAMINER
HUYNH, PHUONG N

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/803,918	Applicant(s) DAYER ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-61* is/are pending in the application.

4a) Of the above claim(s) *1-8,11-14,18-35,44,45 and 50-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,10,15-17,36-43 and 46-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8 & 9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-61 are pending.

2. Applicant's election with traverse of Group II , Claims 9-10, 15-17, 36-43 and 46-49 drawn to a polypeptide, fragments thereof, compositions thereof, and fusion proteins thereof having the sequence of SEQ ID NO: 2, filed 8/7/02, is acknowledged. The traversal is on the grounds that (1) Group I drawn to polynucleotide and Group II drawn to polypeptide is improper and a search for the subject matter of Group I and Groups together would not a serious burden to the examiner. This is not found persuasive because of the reasons set forth in the restriction mailed 4/8/02. A prior art search also requires a literature search. Further, Group I and Group II are drawn to different Class and subclass. A search of Group I would not encompass Group II and vice versa. It is a burden to search more than one invention. Therefore, the requirement of Group II and Groups (I and III-X) is still deemed proper and is therefore made FINAL.

3. Claims 1-8, 11-14, 18-35, 44-45, and 50-61 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 9-10, 15-17, 36-43 and 46-49 are being acted upon in this Office Action.

5. Claims 9-10, and 16 are objected to because said claims depend on non-elected claims 7, 8, and 2, respectively.

6. The disclosure is objected to because of the following informalities: (1) The Brief description of drawing for Figure 5 does not match with the Figure itself; there is no "black columns" in Figures 5, and 6. (2) "A" and "B" have been omitted in the Brief description of drawing of Figure 5. (3) the typographical error "bu" on page 13, line 16 should have been "by" and (4) "75 to 113" on page 5, line 2 should have been "73 to 113". Appropriate action is required.

7. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The recitation of "polypeptide consisting essentially of" in original claim 15 has no

support in the specification as filed. It is suggested that Applicants amend the specification to provide proper antecedent basis for the claimed subject matter.

8. Claim 15 line 8 (e) is objected to because "75 to 113 of SEQ ID NO: 2" should have been "73 to 113 of SEQ ID NO: 2". Correction is required.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 9-10, 15-17, 36-43 and 46-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated polypeptide "consisting of" an amino acid sequence selected from: (a) an amino acid sequence as set forth in residues 25 to 194 of SEQ ID NO: 2; (b) an amino acid sequence as set forth in residues 25 to 144 of SEQ ID NO: 2; (c) an amino acid sequence as set forth in residues 156 to 267 of SEQ ID NO: 2; (d) an amino acid sequence as set forth in residues 25 to 113 of SEQ ID NO: 2; (e) an amino acid sequence as set forth in residues 73 to 113 of SEQ ID NO: 2; (2) an isolated polypeptide encoded by the nucleic acid of SEQ ID NO: 1 and a nucleotide sequence complementary to SEQ ID NO: 2, (3) a polypeptide produced by the process of culturing the host cell which is eukaryotic or prokaryotic under suitable conditions to express the polypeptide and isolating said polypeptide from the culture wherein the host cell comprising the vector comprising the nucleic acid molecule consisting essentially of a nucleotide sequence selected from: (a) the nucleotide sequence as set forth in residues 73 to 601 in SEQ ID NO: 1; (b) the nucleotide sequence encoding the polypeptide as set forth in residues 25 to 194 of SEQ ID NO: 2; (c) the nucleotide sequence as set forth in residues 73 to 451 in SEQ ID NO: 1; (d) the nucleotide sequence encoding the polypeptide as set forth in residues 25 to 144 of SEQ ID NO: 2; (e) the nucleotide sequence as set forth in residues 485 to 820 in SEQ ID NO: 1; (f) the nucleotide sequence encoding the polypeptide as set forth in residues 25 to 113 in SEQ ID NO: 2, (g) the nucleotide sequence encoding the polypeptide as set forth in residues 73 to 113 of SEQ ID NO: 2; (h) the nucleotide sequence encoding the polypeptide as set forth in residues 156 to 267 in SEQ ID NO: 2; (i) the nucleotide sequence complementary to at least one of (a) to (h); (4) a composition comprising the isolated polypeptide "consisting of" an amino acid sequence selected from: (a) an amino acid

sequence as set forth in residues 25 to 194 of SEQ ID NO: 2; (b) an amino acid sequence as set forth in residues 25 to 144 of SEQ ID NO: 2; (c) an amino acid sequence as set forth in residues 156 to 267 of SEQ ID NO: 2; (d) an amino acid sequence as set forth in residues 25 to 113 of SEQ ID NO: 2; (e) an amino acid sequence as set forth in residues 73 to 113 of SEQ ID NO: 2 and a carrier for screening assays, or producing antibody, (5) The isolated polypeptide "consisting of" an amino acid sequence selected from: (a) an amino acid sequence as set forth in residues 25 to 194 of SEQ ID NO: 2; (b) an amino acid sequence as set forth in residues 25 to 144 of SEQ ID NO: 2; (c) an amino acid sequence as set forth in residues 156 to 267 of SEQ ID NO: 2; (d) an amino acid sequence as set forth in residues 25 to 113 of SEQ ID NO: 2; (e) an amino acid sequence as set forth in residues 73 to 113 of SEQ ID NO: 2 wherein the polypeptide is covalently modified with a water-soluble polymer such as the ones recited in claim 41, (6) the isolated polypeptide encoded by the nucleic acid of SEQ ID NO: 1 and a nucleotide sequence complementary to SEQ ID NO: 2 wherein the polypeptide is covalently modified with a water-soluble polymer such as the ones recited in claim 42, (7) a fusion polypeptide comprising the polypeptide "consisting of" an amino acid sequence selected from: (a) an amino acid sequence as set forth in residues 25 to 194 of SEQ ID NO: 2; (b) an amino acid sequence as set forth in residues 25 to 144 of SEQ ID NO: 2; (c) an amino acid sequence as set forth in residues 156 to 267 of SEQ ID NO: 2; (d) an amino acid sequence as set forth in residues 25 to 113 of SEQ ID NO: 2; (e) an amino acid sequence as set forth in residues 73 to 113 of SEQ ID NO: 2 and a heterologous amino acid sequence wherein the heterologous amino cid sequence is an IgG constant domain, (8) a fusion polypeptide comprising the polypeptide encoded by the nucleic acid of SEQ ID NO: 1 and a nucleotide sequence complementary to SEQ ID NO: 2 and a heterologous amino acid sequence wherein the heterologous amino acid sequence is an IgG constant domain for inhibiting the production of IL-1 and TNF alpha in vitro in THP-1 cells activated by membranes of stimulated HUT-78 cells, **does not** reasonably provide enablement for (1) *any* polypeptide produced by the process of culturing the host cell which is a eukaryotic cell comprising the vector comprising the nucleic acid molecule consisting essentially of *any* nucleotide sequence which hybridizes under "moderately or highly stringent conditions" to the complement of any nucleotide sequence of (a) to (F) wherein the encoded polypeptide has *any* activity of the polypeptide as set forth in SEQ I DNO: 2, or *any* nucleotide sequence complementary to the nucleic acid molecule consisting essentially of *any* nucleotide sequence which "hybridizes under moderately or highly stringent conditions" to the complement of any

nucleotide sequence of (a) to (F) wherein the encoded polypeptide has any activity of the polypeptide as set forth in SEQ I DNO: 2, (**2**) *any* polypeptide produced by the process of culturing the host cell, which is a prokaryotic cell, comprising the vector comprising the isolated nucleic acid molecule consisting essentially of a nucleotide sequence selected from: (a) *any* nucleotide sequence consisting essentially of *any* nucleotide sequence that is at least about 70, 75, 80, 85, 95, 96, 97, 98 or 99 percent identical to *any* nucleotide sequences such as the ones recited in claim 1, wherein the nucleotide encodes a polypeptide that has *any* activity of the polypeptide as set forth in SEQ ID NO: 2, (b) *any* nucleotide sequence encoding *any* "allelic variant of splice variant" of *any* nucleotide sequence such as the ones recited in claim 1, wherein the encoded polypeptide has *any* activity of the polypeptide as set forth in SEQ ID NO: 2, (c) *any* nucleotide sequence mentioned above encoding *any* polypeptide of at least about 25 amino acid residues, wherein the polypeptide has *any* activity of the polypeptide as set forth in SEQ ID NO: 2, (d) *any* nucleotide sequence mentioned above "comprising" *any* fragment of at least about 16 nucleotides and (e) *any* nucleotide sequence complementary of *any* of (a), (b) or (c) mentioned above, (**3**) *any* isolated polypeptide "consisting essentially" of *any* amino acid sequence selected from: (a) an amino acids sequence as set forth in residues 25 to 194 of SEQ ID NO: 2; (b) residues 25 to 144 of SEQ ID NO: 2; (c) residues 156 to 267 of SEQ ID NO: 2; (d) residues 25 to 113 of SEQ ID NO: 2; (e) residues 73 to 113 of SEQ ID NO: 2; (f) *any* amino acid sequence for any "ortholog" of SEQ ID NO: 2, wherein the encoded polypeptide has *any* activity of the polypeptide of SEQ ID NO: 2, (g) *any* amino acid sequence that is at least "about 70, 80, 85, 90, 95, 96, 97, 98 or 99 percent identical to any amino acid sequence mentioned in (a), (b) or (c) mentioned above wherein the encoded polypeptide has any activity of the polypeptide of SEQ ID NO: 2, (h) *any* fragment of the amino acid sequence mentioned above "comprising" at least 25 amino acid residues, wherein the encoded polypeptide has any activity of the polypeptide of SEQ ID NO: 2, (i) *any* amino acid sequence for any allelic variant or splice variant of any (a) to (f) mentioned above, wherein the encoded polypeptide has any activity of the polypeptide of SEQ ID NO: 2, (**4**) any isolated polypeptide encode by *any* nucleic acid such as the ones recited in claim 2, (**5**) any isolated polypeptide such as the ones recited in claim 15 wherein the percent identity is determined using a computer program such as the ones recited in claim 17, (**6**) *any* composition comprising *any* polypeptide such as the ones recited in claim 15 or claim 16 and a pharmaceutically acceptable formulation agent wherein the pharmaceutically acceptable formulation comprises at least one of a carrier, adjuvant, solubilizer, stabilizer, or *any* anti-

oxidant for treating any disease, (7) *any* polypeptide such as the ones recited in claim 15 or claim 16 which is covalently modified with any water-soluble polymer, (8) *any* polypeptide such as the ones recited in claim 15 or claim 16 which is covalently modified with a water-soluble polymer such as the ones recited in claims 41 and 43, (9) *any* fusion polypeptide comprising any polypeptide such as the ones recited in claim 15 and *any* heterologous amino acid sequence, (10) *any* fusion polypeptide comprising any polypeptide such as the ones recited in claim 15 or claim 16 and *any* heterologous amino acid sequence wherein the heterologous amino acid sequence is *any* "fragment" of an IgG constant domain for treating any disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only human Apo-A-1 of SEQ ID NO: 2 encoding by the polynucleotide of SEQ ID NO: 1. The full length human Apo-A1 inhibits the production of TNF-α and IL-1β in vitro in THP-1 cells activated by membranes of stimulated HUT-078 cells or antigen-activated peripheral blood monocyte (PBMC) in vitro (See Figures 6-11, page 100). The specification further discloses the inhibitory activity of Apo A-1 corresponds to the fraction on the Western Blot having a molecular weight of 28,000 $\pm$ 10,000 (Fig 6D, page 99 of specification).

With the exception of the full length polypeptide of SEQ ID NO: 2 for inhibiting the production of TNF-α and IL-1β in vitro, the specification does not teach how to make and use *any* polypeptide mentioned above for treating any disease. The term "consisting essentially of" is open-ended. It expands the polypeptide fragment to include additional amino acid residues at either or both ends and the corresponding nucleotide sequence encoding the additional amino acids at either or both ends. The state of the art recognizes that sequence identity does not predict biological function. It is known in the art that even single amino acid changes or differences in a

protein's amino acid sequence can have dramatic effects on the protein's function. For example, Mikayama *et al* teach that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (Figure 1 in particular). Yet, Mikayama *et al.* teach further that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF bioactivity (Abstract in particular). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet *et al* teach that a single Glu to Val substitution in the subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, paragraph bridging columns in particular). Given the indefinite number of undisclosed polypeptide and the corresponding nucleotides for the additional amino acids, there is insufficient guidance as to the specific amino acids should be added, and whether the resulting polypeptide after modification will still retain the structural and functional properties as SEQ ID NO: 2, in turn, suitable for pharmaceutical use. As such, further research would be required to identify the fragment having the specific activity as the full length polypeptide of SEQ ID NO: 2, in turn, for treating a specific disease.

Further, there is insufficient working examples of any fragment has any activity, much less treating any disease using any fragment such as the ones recited in claims 9-10, 15-17. Even if the polypeptide is full length, there is no in vivo working example that the claimed polypeptide can treat any disease. A pharmaceutical composition in the absence of in vivo data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

With regard to polypeptide produced by the nucleic acid molecule consisting essentially of *any* nucleotide sequence which hybridizes under "moderately or highly stringent conditions" to

the complement of *any* nucleotide sequence such as the ones recited (a) to (F) of claim 1 wherein the encoded polypeptide has *any* activity of the polypeptide as set forth in SEQ I DNO: 2, or *any* nucleotide sequence complementary to the nucleic acid molecule consisting essentially of *any* nucleotide sequence which "hybridizes under moderately or highly stringent conditions" to the complement of any nucleotide sequence of (a) to (F) wherein the encoded polypeptide has any activity of the polypeptide as set forth in SEQ I DNO: 2, the specification does not disclose the specific conditions used by applicants such as salt concentration, melting and annealing temperature and the duration of hybridization for the specific polynucleotide encoding the specific polypeptide. The state of the prior art as exemplified by Wallace *et al* is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. Furthermore, a database search was done for 20mers of the specified sequence, the total number of hits was 143,797,728 which suggest that some of the polynucleotides encompassed by the claims would not preferentially hybridize to SEQ ID NO: 1. Further, the term "consisting essentially of" is open-ended. It expands the polypeptide, the corresponding polynucleotide to include additional nucleotide at either or both ends. Given the number of undisclosed polynucleotide, it is unpredictable which undisclosed polynucleotide would hybridize specifically to a polynucleotide encoding a polypeptide having additional undisclosed amino acids, much less having a specific activity such as inhibition of TNFα and IL-1β production, in turn, would be useful for treating any disease.

With regard to claim 10 which recites a polypeptide produced by a polynucleotide sequence consisting of a nucleotide sequence that is at least "about 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99 percent identical to the nucleotide sequence such as the ones recited in claim 1, wherein the polynucleotide sequence has any activity as set forth in SEQ ID NO: 2, the specification discloses only human Apo A-1 comprising SEQ ID NO: 2 encoded by of a polynucleotide of SEQ ID NO: 1 and a fragment of human Apo A-1 encoded by polynucleotide sequence consisting of SEQ ID NO: 4. The specification does not disclose any polypeptide encoding by a polynucleotide sequence consisting of a nucleotide sequence that is at least "about 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99 percent identical to the nucleotide sequence, much less demonstrating having any activity. Attwood *et al* teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable. Thus, knowing structure alone will not inherently tell us function (See figure, entire document). Given the

indefinite number of polypeptide with undisclosed functions, it follows that any polypeptide for inhibiting the production of IL-1 TNFα and IL-1β is not enabled.

With regard to polypeptide produced by polynucleotide encoding an "allelic variant" or "splice variant" of any polynucleotide according to claim 1, the specification discloses only human Apo A-1 comprising SEQ ID NO: 2 encoded by a polynucleotide of SEQ ID NO: 1 and a fragment of human Apo A-1 encoded by polynucleotide sequence consisting of SEQ ID NO: 4. The specification defines "AFTI polypeptide allelic variant" on page 14 as several or many possible naturally occurring alternative forms of a gene occupying a given locus on a chromosome of any organisms or a population of organisms. There is insufficient guidance and working example demonstrating any "allelic variant" or "splice variant" having the same activity as the claimed polypeptide of SEQ ID NO: 2, much less treating any disease.

With regard to a polypeptide produced by polynucleotide such as the ones recited in claim 2(d) "comprising" a fragment of at least about 16 nucleotides, the term "comprising" is open-ended. It expands the nucleotide to include additional nucleotide to either or both ends of polynucleotide. There is insufficient guidance and working example demonstrating any undisclosed polypeptide encoding by any undisclosed polynucleotide having additional nucleotide would have the same structure and functions as polypeptide of SEQ ID NO: 2. Even if the polypeptide encoding by the polynucleotide is limited to 16 nucleotides, there is insufficient guidance which fragment within the full length of polynucleotide encoding the fragment of polypeptide of SEQ ID NO: 2 would have the same activity as the full length polypeptide of SEQ ID NO: 2. Further, a 16 polynucleotides encoded a polypeptide of only four amino acids in length, there is no working example demonstrating any polypeptide having only 4 amino acids in length has any activity as the claimed polypeptide of SEQ ID NO: 2 such as inhibiting the production of IL-1 TNFα and IL-1β in vitro. Since the polypeptide encoding by the polynucleotide mentioned above is not enabled, it follows that any nucleotide sequence complement to any undisclosed nucleotide mentioned above is not enabled.

With regard to "ortholog" of SEQ ID NO: 2 having an activity of the polypeptide of SEQ ID NO: 2, the specification on page 15 defines "ortholog" as any polypeptide from another species that corresponds to an AFTI polypeptide of SEQ ID NO: 2. The specification discloses only human AFTI of SEQ ID NO: 2. There is no other polypeptide in the specification that is an ortholog of human Apo A-I, let alone having the same activity such as the claimed polypeptide of SEQ ID NO: 2. Given the indefinite number of undisclosed ortholog of SEQ ID NO: 2 from any

other species, it is unpredictable which undisclosed amino acid sequence of any ortholog of SEQ ID NO: 2 will have the same structure, much less the activity as SEQ ID NO: 2, in turn, would be useful for any purpose.

With regard to an isolated polypeptide "consisting essentially of" an amino acid sequence that is at least about "about 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence as set forth in residues 25 to 194 of SEQ ID NO: 2, residues 25 to 144 of SEQ ID NO: 2, or residues 156 to 267 of SEQ ID NO: 2, wherein the polypeptide sequence has any activity as set forth in SEQ ID NO: 2, the specification discloses only human Apo A-1 comprising SEQ ID NO: 2 that inhibits the production of TNFα and IL-1β. The specification does not teach any other polypeptide having any sequence identity with SEQ ID NO: 2, let alone having the same function as the claimed sequence of SEQ ID NO: 2. Further, the term "consisting essentially of" is open-ended. It expands the polypeptide to include additional amino acid residues at either or both ends in addition to having various percent identities. Given the indefinite undisclosed polypeptide, it is unpredictable which undisclosed polypeptide would have the same functions as polypeptide of SEQ ID NO: 2. Although sequence alignment using various computer program such as the ones recited in claim 17 is known in the art, sequence identity is not equal having the same function.

Attwood *et al* teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable. Thus, knowing structure alone will not inherently tell us function (See figure, entire document). Given the functions of any polypeptide mentioned above, it follows that any polypeptide for inhibiting the production of IL-1 TNFα and IL-1β is not enabled. The specification does not disclose whether any allelic variant have the same activity much less having the same structure. Since the allelic variant and splice variant are not enabled, it follows that any fragment of any disclosed allelic variant and splice variant are not enabled

With regard to fragment "comprising" at least about 25 amino acid residues as recited in claim 15 (h), the term "comprising" is open-ended. It expands the fragment to include additional undisclosed amino acid residues at either or both ends in addition to residues 25 to 194 of SEQ ID NO: 2, residues 25 to 144 of SEQ ID NO: 2, or residues 156 to 267 of SEQ ID NO: 2 which already recited in the claim. There is insufficient guidance as the specific amino acids that can be added or modified such that after addition would retain structure and activity as SEQ ID NO: 2.

There is no working example demonstrating any fragment has any activity. Not only the amino acid sequence that is an ortholog of SEQ ID NO: 2 not disclosed, it is unpredictable which fragment "comprising" the undisclosed ortholog of SEQ ID NO: 2 would have the same activity as SEQ ID NO: 2. Likewise, there is insufficient guidance and working example demonstrating any fragment of any amino acid sequence that is about 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence as set forth in residues 25 to 194 of SEQ ID NO: 2, residues 25 to 144 of SEQ ID NO: 2, or residues 156 to 267 of SEQ ID NO: 2 having the same activity as SEQ ID NO: 2. Since the polypeptides are not enabled, it follows that polypeptides covalently modified with any water-soluble polymer such as the ones recited in claims 41 and 43 are not enabled. It also follows that any composition comprising any undisclosed polypeptide are not enabled. It also follows that any fusion polypeptide comprising any undisclosed amino acid sequence mentioned above and any heterologous amino acid sequence is not enabled. Further, the term "heterologous amino acid sequence" could be any undisclosed sequence. Given the indefinite number of undisclosed "heterologous amino acid sequence", it is unpredictable which fusion protein comprising any undisclosed "heterologous amino acid sequence" and polypeptide such as the ones recited in claim 15 would have the same function as SEQ ID NO: 2, in turn, would be useful for any purpose.

For these reasons, it would require undue experimentation even for one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

11. Claims 9-10, 15-17, 36-43 and 46-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* polypeptide produced by the process of culturing the host cell which is a eukaryotic cell comprising the vector comprising the nucleic acid molecule consisting essentially of *any* nucleotide sequence which hybridizes under "moderately or highly stringent conditions" to the complement of any nucleotide sequence of (a) to (F) wherein the encoded polypeptide has *any* activity of the polypeptide as set forth in SEQ I DNO: 2, or *any* nucleotide sequence complementary to the nucleic acid molecule consisting essentially of *any* nucleotide sequence which "hybridizes under moderately or highly stringent conditions" to the complement of any nucleotide sequence of (a) to (F) wherein the encoded polypeptide has any activity of the polypeptide as set forth in SEQ I DNO: 2, (2) *any* polypeptide produced by the process of culturing the host cell, which is a prokaryotic cell, comprising the vector comprising the isolated nucleic acid molecule consisting essentially of a nucleotide sequence selected from: (a) *any* nucleotide sequence consisting essentially of *any* nucleotide sequence that is at least about 70, 75, 80, 85, 95, 96, 97, 98 or 99 percent identical to *any* nucleotide sequences such as the ones recited in claim 1, wherein the nucleotide encodes a polypeptide that has *any* activity of the polypeptide as set forth in SEQ ID NO: 2, (b) *any* nucleotide sequence encoding *any* "allelic variant of splice variant" of *any* nucleotide sequence such as the ones recited in claim 1, wherein the encoded polypeptide has *any* activity of the polypeptide as set forth in SEQ ID NO: 2, (c) *any* nucleotide sequence mentioned above encoding *any* polypeptide of at least about 25 amino acid residues, wherein the polypeptide has *any* activity of the polypeptide as set forth in SEQ ID NO: 2, (d) *any* nucleotide sequence mentioned above "comprising" *any* fragment of at least about 16 nucleotides and (e) *any* nucleotide sequence complementary of *any* of (a), (b) or (c) mentioned above, (3) *any* isolated polypeptide "consisting essentially" of *any* amino acid sequence selected from: (a) an amino acids sequence as set forth in residues 25 to 194 of SEQ ID NO: 2; (b) residues 25 to 144 of SEQ ID NO: 2; (c) residues 156 to 267 of SEQ ID NO: 2; (d) residues 25 to 113 of SEQ ID NO: 2; (e) residues 73 to 113 of SEQ ID NO: 2; (f) *any* amino acid sequence for any "ortholog" of SEQ ID NO: 2, wherein the encoded polypeptide has *any* activity of the polypeptide of SEQ ID NO: 2, (g) *any* amino acid sequence that is at least "about 70, 80, 85, 90, 95, 96, 97, 98 or 99 percent identical to any amino acid sequence mentioned in (a), (b) or (c) mentioned above wherein the encoded polypeptide has any activity of the polypeptide of SEQ ID NO: 2, (h) *any* fragment of the amino acid sequence mentioned above "comprising" at least 25 amino acid residues, wherein the encoded polypeptide has any activity of the polypeptide of SEQ ID NO: 2,

(i) *any* amino acid sequence for any allelic variant or splice variant of any (a) to (f) mentioned above, wherein the encoded polypeptide has any activity of the polypeptide of SEQ ID NO: 2, **(4)** any isolated polypeptide encode by *any* nucleic acid such as the ones recited in claim 2, **(5)** any isolated polypeptide such as the ones recited in claim 15 wherein the percent identity is determined using a computer program such as the ones recited in claim 17, **(6)** *any* composition comprising *any* polypeptide such as the ones recited in claim 15 or claim 16 and a pharmaceutically acceptable formulation agent wherein the pharmaceutically acceptable formulation comprises at least one of a carrier, adjuvant, solubilizer, stabilizer, or *any* anti-oxidant for treating any disease, **(7)** *any* polypeptide such as the ones recited in claim 15 or claim 16 which is covalently modified with any water-soluble polymer, **(8)** *any* polypeptide such as the ones recited in claim 15 or claim 16 which is covalently modified with a water-soluble polymer such as the ones recited in claims 41 and 43, **(9)** *any* fusion polypeptide comprising any polypeptide such as the ones recited in claim 15 and *any* heterologous amino acid sequence, **(10)** *any* fusion polypeptide comprising any polypeptide such as the ones recited in claim 15 or claim 16 and *any* heterologous amino acid sequence wherein the heterologous amino acid sequence is *any* "fragment" of an IgG constant domain for treating any disease.

The specification discloses only human Apo-A-1 of SEQ ID NO: 2 encoding by the polynucleotide of SEQ ID NO: 1. The specification further discloses the full length human Apo-A1 inhibits the production of TNF-α and IL-1β in vitro in THP-1 cells activated by membranes of stimulated HUT-078 cells or antigen-activated peripheral blood monocyte (PBMC) in vitro (See Figures 6-11, page 100). The specification discloses the inhibitory activity of Apo A-1 corresponds to the fraction on the Western Blot having a molecular weight of 28,000 ± 10,000 (Fig 6D, page 99 of specification).

With the exception of the specific polypeptide mentioned above for inhibiting the production of TNF-α and IL-1β in vitro, there is insufficient written description about the structure associated with function of *any* isolated polypeptide "consisting essentially" of *any* amino acid sequence selected from: (a) an amino acids sequence as set forth in residues 25 to 194 of SEQ ID NO: 2; (b) residues 25 to 144 of SEQ ID NO: 2; (c) residues 156 to 267 of SEQ ID NO: 2; (d) residues 25 to 113 of SEQ ID NO: 2; (e) residues 73 to 113 of SEQ ID NO: 2; (f) *any* "ortholog" of SEQ ID NO: 2, *any* amino acid sequence that is at least "about 70, 80, 85, 90, 95, 96, 97, 98 or 99 percent identical to any amino acid sequence mentioned in (a), (b) or (c) mentioned above. The term "consisting essentially of" or "comprising" is open-ended. It

expands the polypeptide to include additional amino acids at either or both ends, and the corresponding polynucleotide encoding the additional amino acids.

Further, the specification discloses only human Apo A-1 of SEQ ID NO: 2 that inhibit the production of TNF-α and IL-1β in vitro. Given the lack of a written description of *any* additional representative species of polypeptide of Apo A-1, *any* ortholog of SEQ ID NO: 2, *any* amino acid sequence that is at least "about 70, 80, 85, 90, 95, 96, 97, 98 or 99 percent identical" to *any* amino acid sequence mentioned in (a), (b) or (c) mentioned above and *any* polypeptide produced by *any* polynucleotide encoding said polypeptides, *any* fusion polypeptide, *any* composition comprising *any* polypeptide mentioned above for treating any disease, *any* polypeptide modified with *any* water-soluble polymer, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

13. Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "wherein the encoded polypeptide" in claim 15 (f) line 2 is ambiguous. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention. Since only polynucleotide encodes a polypeptide, it is suggested that the term "encoded" be deleted.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in-
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

15. Claims 15 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,408,038 (April 1995, PTO 892).

The '038 patent teaches a fusion polypeptide such as A-I/B-100 comprising the polypeptide consisting of an amino acid sequence that is 100 percent identical an amino acid sequence from residue 25 to 144 of the claimed SEQ ID NO: 2 fused to a heterologous sequence such as the reference SEQ ID NO: 1 (Apo B-100) (See claims 10-12 of '038 patent, in particular). The '038 patent further teaches a fusion polypeptide of Apo A-I from about 19 residue through about 250 of the reference SEQ ID NO: 3, which is consisting essentially of residues 25 to 194 of the claimed SEQ ID NO: 2 fused to apo B-100 from about residue 3430 through about residue 3520 of the reference SEQ ID NO: 1 (See column 7, lines 6-11, in particular). The '038 patent teaches the entire reference apo A-I amino acid sequence or a fragment of the reference apo A-I, can be fused to apo B-100 (See column 16, lines 7, in particular). The term "consisting essentially of" and "comprising" is open-ended. It expands the claimed polypeptide and fragment to include additional amino acids residues at either or both ends to include the reference polypeptide of SEQ ID NO: 3 and fragment thereof. The reference polypeptide of SEQ ID NO: 3 inherently has the same activity as the claimed SEQ ID NO: 2 since it is identical to the claimed SEQ ID NO: 2. Thus, the reference teachings anticipate the claimed invention.

16. Claims 10, 15-17, 46 and 48 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 5,721,114 (Feb 1998, PTO 892).

The '114 patent teaches a polypeptide such as Apo A-I-M (Milano) that is 91 % identical to the claimed polypeptide of SEQ ID NO: 2 produced by host cell comprising the vector comprising the reference polynucleotide (See abstract, reference SEQ ID NO: 6, claims of '114, in particular). The '114 patent further teaches polypeptide fragment such as the C terminal fragment from residues 185 to 243 of reference SEQ ID NO: 6, which is at least 25 amino acid residues (instant Claim 15 h, See column 11, lines 10-23, in particular). The '114 patent further teaches chimeric protein (fusion protein) such as Apo AI moiety or the prosequence of human

Apo AI fused to the N-terminal amino acid residues of heterologous sequence such as β-galactosidase or to one or more IgG binding domains of protein A (See column 2, lines 7-12, in particular). Claim 17 is included in this rejection because a product is a product irrespective of how it is made or identified. Thus, the reference teachings anticipate the claimed invention.

17. Claims 9-10, 15, 16, 17 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 96/37608 (Nov 1996, PTO 1449).

The WO 96/37608 publication teaches a pharmaceutical composition comprising a polypeptide encoded by the nucleic acid molecule consisting essentially of a nucleotide sequence encoding a polypeptide of at least about 25 amino acid residues (See abstract, reference SEQ ID NO: 10, in particular). The WO 96/37608 publication teaches various allelic variants such as Milano having a mutation such as an arginine substitute for Cys at 173 and another variant possesses a replacement of the arginine residue at position 151 of the mature apoA-I polypeptide by a cysteine residue, which corresponding to position 175 in the prepro apo A-I of the reference SEQ ID NO: 2 (See claim 2 of WO 96/37608 publication, Table on page 2, in particular). The reference polypeptide of SEQ ID NO: 2 is encoded by a polynucleotide which hybridizes to the complement of an isolated nucleic acid molecule encoding a polypeptide that is 100% identical to the claimed polypeptide of SEQ ID NO: 2 (See page 20, lines 5-9, example 2 on page 19, in particular). Claims 9-10 and 17 are included in this rejection because a product is a product irrespective of how it is made or identified. Thus, the reference teachings anticipate the claimed invention.

18. Claims 9-10, 15, 16, 17 and 36 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No. 6,258,596 B1 (July 2001, PTO 892).

The '596 patent teaches various allelic variants such as Milano having a mutation such as an arginine substitute for Cys at 173 and another variant possesses a replacement of the arginine residue at position 151 of the mature apoA-I polypeptide by a cysteine residue, which corresponding to position 175 in the prepro apo A-I of the reference SEQ ID NO: 2 (See column 2, lines 15-16, lines in particular). The reference polypeptide of SEQ ID NO: 2 is encoded by a polynucleotide which hybridizes to the complement of an isolated nucleic acid molecule encoding a polypeptide that is 100% identical to the claimed polypeptide of SEQ ID NO: 2 (See column 3, lines 20-26, column 11, example 2, in particular). The '596 patent further teaches a polypeptide

encoded by a nucleic acid molecule consisting essentially of a nucleotide comprising a fragment of least about 16 nucleotide in length (See reference SEQ ID NOS: 10 and 12 for polynucleotide encoding the reference polypeptide of SEQ ID NO: 11 and 13, respectively, column 12, lines 14-15, lines 26-27, in particular). The '596 patent further teaches a composition comprising the reference polypeptide (See abstract, in particular). Claims 9-10 and 17 are included in this rejection a product is a product, irrespective of how it is made or identified. Thus, the reference teachings anticipate the claimed invention.

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 15, 46 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,408,038 (April 1995, PTO 892) in view of US Pat 5,116,964 (May 1992; PTO 892).

The teachings of the '038 patent have been discussed supra. The '038 patent further teaches apoA-I is unstable (see column 2, lines 6-8, in particular).

The claimed invention as recited in claim 47 differs from the reference only that the fusion polypeptide wherein the heterologous amino acid sequence is an IgG constant or fragment thereof.

The '964 patent teaches immunoglobulin fusion polypeptide such as CH2 and CH3 domains of the constant region of an immunoglobulin or fragment thereof fused to any polypeptide of interest such as LHR (See abstract, column 10, lines 10-16, in particular). The

advantage of immunoglobulin fusion polypeptide extends the half-lives of the fusion protein and useful in therapeutic or diagnostic (See column 8, lines 10-34, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the LHR of the immunoglobulin fusion polypeptide as taught by the '964 patent or the B-100 polypeptide in the A-I/B-100 fusion protein as taught by the '038 patent for a fusion protein comprising apo A-I fused to IgG constant or fragment thereof as taught by the '038 patent and the '964 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '038 patent teaches apoA-I is unstable (see column 2, lines 6-8, in particular). The '964 patent teaches immunoglobulin fusion polypeptide extends the half-lives of the fusion protein and useful in therapeutic or diagnostic (See column 8, lines 10-34, in particular).

22. Claims 15, 16, and 46-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,721,114 (Feb 1998, PTO 892) in view of US Pat 5,116,964 (May 1992; PTO 892).

The teachings of the '114 patent have been discussed supra.

The claimed invention as recited in claims 46 and 48 differs from the reference only that the fusion polypeptide comprising a heterologous amino acid sequence.

The claimed invention as recited in claims 47 and 49 differs from the reference only that the fusion polypeptide wherein the heterologous amino acid sequence is an IgG constant or fragment thereof.

The '964 patent teaches immunoglobulin fusion polypeptide such as CH2 and CH3 domains of the constant region of an immunoglobulin or fragment thereof fused to any polypeptide of interest such as LHR (See abstract, column 10, lines 10-16, in particular). The advantage of immunoglobulin fusion polypeptide extends the half-lives of the fusion protein and useful in therapeutic or diagnostic (See column 8, lines 10-34, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the LHR of the immunoglobulin fusion polypeptide as taught by the '964 patent for the Apo A-I-M (Milano) or the polypeptide fragment such as the C terminal fragment from residues 185 to 243 of reference SEQ ID NO: 6 as taught by the '114 patent for a fusion protein comprising Apo A-I-M (Milano) or polypeptide fragment such as the C terminal

fragment from residues 185 to 243 of reference SEQ ID NO: 6 fused to IgG constant or fragment thereof as taught by the '114 patent and the '964 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '964 patent teaches immunoglobulin fusion polypeptide extends the half-lives of the fusion protein and useful in therapeutic or diagnostic (See column 8, lines 10-34, in particular).

23. Claims 15, 16, and 46-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/37608 (Nov 1996, PTO 1449) or US Pat No. 6,258,596 B1 (July 2001, PTO 892) each in view of US Pat 5,116,964 (May 1992; PTO 892).

The teachings of the WO 96/37608 publication and the '596 patent have been discussed supra.

The claimed invention as recited in claims 46 and 48 differs from the reference only that the fusion polypeptide comprising a heterologous amino acid sequence.

The claimed invention as recited in claims 47 and 49 differs from the references only that the fusion polypeptide wherein the heterologous amino acid sequence is an IgG constant or fragment thereof.

The '964 patent teaches immunoglobulin fusion polypeptide such as CH2 and CH3 domains of the constant region of an immunoglobulin or fragment thereof fused to any polypeptide of interest such as LHR (See abstract, column 10, lines 10-16, in particular). The advantage of immunoglobulin fusion polypeptide extends the half-lives of the fusion protein and useful in therapeutic or diagnostic (See column 8, lines 10-34, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the LHR of the immunoglobulin fusion polypeptide as taught by the '964 patent for the allelic variants such as Milano or the polypeptide fragment encoded by the polynucleotide comprising at least about 16 nucleotides as taught by the '596 and the WO 96/37608 publication for a fusion protein comprising the allelic variants such as Milano or the polypeptide fragment encoded by the polynucleotide comprising at least about 16 nucleotides fused to IgG constant or fragment thereof as taught by the WO 96/37608 publication, the '596 patent and the '964 patent. From the combined teachings of the references, it is

apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '964 patent teaches immunoglobulin fusion polypeptide extends the half-lives of the fusion protein and useful in therapeutic or diagnostic (See column 8, lines 10-34, in particular).

24. Claims 15, 36, 38, 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,408,038 (April 1995, PTO 892) in view of US Pat No. 5,824,784 (Oct 1998; PTO 892).

The teachings of the '038 patent have been discussed supra.

The claimed invention in claim 38 differs from the reference only that composition wherein the pharmaceutically acceptable formulation agent comprises at least one of a carrier, adjuvant, solubilizer, stabilizer or anti-oxidant.

The claimed invention as recited in claim 40 differs from the reference only that polypeptide is covalently modified with a water-soluble polymer.

The claimed invention as recited in claim 41 differs from the reference only that polypeptide is covalently modified with a water soluble polymer wherein the water soluble polymer is selected from polyethylene glycol, monomethoxy polyethylene glycol, dextran, cellulose, poly(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohol.

The '784 patent teaches method and composition for covalently modified any polypeptide of interest such as G-CSF or INF with a water-soluble polymer such as polyethylene glycol, monomethoxy polyethylene glycol, dextran, cellulose, poly(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohol (See abstract, column 6, lines 32-67 bridging column 7, lines 1-5, column 9, lines 64-66, in particular). The '1784 patent further teaches pharmaceutically acceptable formulation agent such as carrier such as phosphate buffer, adjuvant, solubilizer such as Tween 80, anti-oxidants such as ascorbic acid, and sodium metafisulfate (See column 11, lines 11-32, in particular). The '784 patent teaches the advantages of N-terminally pegylated protein provides a homogeneous preparation to ease in clinical application in predictability of lot to lot pharmacokinetics, for desired dosage, increasing circulation time such as sustained release and resistance to proteolysis and other consideration

such as lack of antigenicity (See column 5, lines 29-35, column 6, lines 44-48, column 7, lines 1-5, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently modified the A-I/B-100 fusion protein as taught by the '038 patent using water soluble polymer as taught by the '784 patent for a water-soluble polymer modified A-I/B-100 as taught by the '038 patent and the '784 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '038 patent teaches apoA-I is unstable (see column 2, lines 6-8, in particular). The '784 patent teaches the advantages of N-terminally pegylated protein provides a homogeneous preparation to ease in clinical application in predictability of lot to lot pharmacokinetics, for desired dosage, increasing circulation time such as sustained release and resistance to proteolysis and other consideration such as lack of antigenicity (See column 5, lines 29-35, column 6, lines 44-48, column 7, lines 1-5, in particular).

25. Claims 15, 16, and 36-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,721,114 (Feb 1998, PTO 892) in view of US Pat No. 5,824,784 (Oct 1998; PTO 892).

The teachings of the '114 patent have been discussed supra.

The claimed invention in claims 38 and 39 differs from the reference only that composition wherein the pharmaceutically acceptable formulation agent comprises at least one of a carrier, adjuvant, solubilizer, stabilizer or anti-oxidant.

The claimed invention as recited in claims 40 and 42 differs from the reference only that polypeptide is covalently modified with a water-soluble polymer.

The claimed invention as recited in claims 41 and 43 differs from the reference only that polypeptide is covalently modified with a water soluble polymer wherein the water soluble polymer is selected from polyethylene glycol, monomethoxy polyethylene glycol, dextran, cellulose, poly(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohol.

The '784 patent teaches method and composition for covalently modified any polypeptide of interest such as G-CSF or INF with a water-soluble polymer such as polyethylene

glycol, monomethoxy polyethylene glycol, dextran, cellulose, poly(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohol (See abstract, column 6, lines 32-67 bridging column 7, lines 1-5, column 9, lines 64-66, in particular). The '784 patent further teaches pharmaceutically acceptable formulation agent such as carrier such as phosphate buffer, adjuvant, solubilizer such as Tween 80, anti-oxidants such as ascorbic acid, and sodium metafisulfate (See column 11, lines 11-32, in particular). The '784 patent teaches the advantages of N-terminally pegylated protein provides a homogeneous preparation to ease in clinical application in predictability of lot to lot pharmacokinetics, for desired dosage, increasing circulation time such as sustained release and resistance to proteolysis and other consideration such as lack of antigenicity (See column 5, lines 29-35, column 6, lines 44-48, column 7, lines 1-5, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently modified the Apo A-I-M (Milano) or the polypeptide fragment such as the C terminal fragment from residues 185 to 243 of reference SEQ ID NO: 6 as taught by the '114 patent using water soluble polymer as taught by the '784 patent for a water-soluble polymer modified the Apo A-I-M (Milano) or the polypeptide fragment such as the C terminal fragment from residues 185 to 243 of reference SEQ ID NO: 6 as taught by the '114 patent and the '784 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '784 patent teaches the advantages of N-terminally pegylated protein provides a homogeneous preparation to ease in clinical application in predictability of lot to lot pharmacokinetics, for desired dosage, increasing circulation time such as sustained release and resistance to proteolysis and other consideration such as lack of antigenicity (See column 5, lines 29-35, column 6, lines 44-48, column 7, lines 1-5, in particular).

26. Claims 15, 16, and 36-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/37608 (Nov 1996, PTO 1449) or US Pat No. 6,258,596 B1 (July 2001, PTO 892) each in view of US Pat No. 5,824,784 (Oct 1998; PTO 892).

The teachings of the WO 96/37608 publication and the '596 patent have been discussed supra.

The claimed invention in claims 38 and 39 differs from the references only that composition wherein the pharmaceutically acceptable formulation agent comprises at least one of a carrier, adjuvant, solubilizer, stabilizer or anti-oxidant.

The claimed invention as recited in claims 40 and 42 differs from the references only that polypeptide is covalently modified with a water-soluble polymer.

The claimed invention as recited in claims 41 and 43 differs from the references only that polypeptide is covalently modified with a water soluble polymer wherein the water soluble polymer is selected from polyethylene glycol, monomethoxy polyethylene glycol, dextran, cellulose, poly(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohol.

The '784 patent teaches method and composition for covalently modified any polypeptide of interest such as G-CSF or INF with a water-soluble polymer such as polyethylene glycol, monomethoxy polyethylene glycol, dextran, cellulose, poly(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohol (See abstract, column 6, lines 32-67 bridging column 7, lines 1-5, column 9, lines 64-66, in particular). The '784 patent further teaches pharmaceutically acceptable formulation agent such as carrier such as phosphate buffer, adjuvant, solubilizer such as Tween 80, anti-oxidants such as ascorbic acid, and sodium metafisulfate (See column 11, lines 11-32, in particular). The '784 patent teaches the advantages of N-terminally pegylated protein provides a homogeneous preparation to ease in clinical application in predictability of lot to lot pharmacokinetics, for desired dosage, increasing circulation time such as sustained release and resistance to proteolysis and other consideration such as lack of antigenicity (See column 5, lines 29-35, column 6, lines 44-48, column 7, lines 1-5, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently modified the allelic variants such as Milano or the polypeptide fragment encoded by the polynucleotide comprising at least about 16 nucleotides as taught by the '596 and the WO 96/37608 publication for a water-soluble polymer modified the allelic variants such as Milano or the polypeptide fragment encoded by the polynucleotide comprising at least

about 16 nucleotides as taught by the '596 and the WO 96/37608 publication and the '784 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '784 patent teaches the advantages of N-terminally pegylated protein provides a homogeneous preparation to ease in clinical application in predictability of lot to lot pharmacokinetics, for desired dosage, increasing circulation time such as sustained release and resistance to proteolysis and other consideration such as lack of antigenicity (See column 5, lines 29-35, column 6, lines 44-48, column 7, lines 1-5, in particular).

27. No claim is allowed.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

29. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
October 21, 2002

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